REMARKS/ARGUMENTS.

Amendments to the Claims.

The listing of claims will replace all prior versions, and listings, of claims in the application. Revised claims are submitted, in which claim 26 has been amended to include the features of claim 27, and claim 27 cancelled, as described in Section (3) below.

1. DOUBLE PATENTING.

Claims 1, 3, 14, 17, 18, 26-28, 30 and 31 stand provisionally rejected in this regard with respect to co-pending application 11/815360.

Applicants note the rejection, and will file a suitable terminal disclaimer when the current claims are deemed allowable.

2. CLAIM REJECTIONS: 35 USC §103.

2.1 Lee, Haberkorn, Colucci and Flanagan.

The previous rejection to Claims 1, 3, 14, 17-18, 26-28 and 31 is maintained.

The Examiner's argument is based on the supposition that the person skilled in the art would ignore the clear conclusion of Haberkorn (quoted previously) that caspase substrates, not caspase inhibitors, are the way to obtain a suitable imaging agent for apoptosis. The Examiner argues that the person skilled in the art would instead, be motivated to use the

teaching on Haberkorn on the concentration of activated caspases being unknown, and choose a reversible inhibitor approach.

Applicants respectfully request the Office provide the page and line citation in Haberkorn where the information on the concentration of activated caspases being unknown is to be found – since Applicants cannot locate it.

The fact is, however, that Haberkorn *et al* were already aware of such information (they cited it in their own publication), and still recommended caspase substrates (not reversible caspase inhibitors) as the way forward. Applicants refer to the Discussion (pages 796-797) and Abstract (page 793) of Haberkorn, where the (very) clear teaching on substrates rather than inhibitors is provided. The Examiner's argument thus clearly involves not only a contradiction of the Discussion and Abstract of Haberkorn itself, but an insertion of information (extending the thinking to radiolabelled reversible caspase inhibitors) on which Haberkorn itself is silent. On both counts this is evidence of an invalid hindsight approach. The combination [Haberkorn + Lee] is therefore believed invalid, and should be withdrawn.

The Examiner also refers to Colucci at [0274] for a teaching on the use of ^{125}I-M808 *in vivo*. That section of text from Colucci includes the statement:

> "However, in contrast to protein extract and whole cell labeling, the intensity of the p17 signal was not proportional to the amount of p17 caspase-3 present."

and:

> "As such, even though [^{125}I]-M808 detects active caspase *in vivo*, its usefulness is limited to systems where tissues are equally well perfused in all animals."

Thus, Colucci itself teaches very clearly that [^{125}I]-M808 has "limited" usefulness *in vivo*, and in fact only to the situation where tissues are equally well perfused. Applicants contend that the person skilled in the art could have no motivation to use Colucci in the manner suggested by the Examiner (i.e. to go to the trouble of making ^{123}I-analogues), since the clear teaching of Colucci itself is that the compound itself has limited usefulness, and that the limited application (i.e. equal perfusion of tissues) is an artificial situation which is unrealistic where faced with an intact mammalian subject for medical imaging. The rejection based on [Haberkorn + Lee + Colucci] should therefore also be withdrawn.

2.2 Lee, Haberkorn, Colucci, Flanagan and Hunter.

Claims 1, 3, 14, 17-18, 26-28 and 31 stand newly rejected as obvious over the combination Lee, Haberkorn, and Colucci, further in view of Flanagan and Hunter.

The Examiner's argument is that Haberkorn teaches that an ^{131}I-labelled caspase-3 inhibitor "…may be useful in imaging of apoptosis."

Applicants respectfully point out that, as argued in 2.1 above, this represents a clear contradiction of Haberkorn itself. The whole point of the Haberkorn paper is the report that, whilst the inhibitor approach *seemed* attractive, in practice i.e. when tested out experimentally, it did not work. That led Haberkorn to conclude that the substrate approach

should be used instead. It would not be practical for the person skilled in the art to combine references on the basis of a teaching demonstrated by Haberkorn not to work.

The Examiner has failed to demonstrate why the person skilled in the art would definitely ignore the clear conclusion and experimental evidence of lack of success provided by Haberkorn. Applicants contend that the prior art references must be properly construed as to what they teach the person skilled in the art in the absence of the teaching of the present invention. The Examiner cannot apply a teaching to a document which contradicts the document itself, nor can any alleged motivation be based on such a clear contradiction. Hence, the rejection based on the combinations [Lee + Haberkorn], [Lee + Haberkorn + Flanagan] and [Lee + Haberkorn + Flanagan + Hunter] should be withdrawn.

The Examiner also bases the alleged motivation on Colucci. Applicants refer to their arguments in 2.1 above, where Colucci also is shown to teach that the compounds therein only have "limited" application under defined circumstances *in vivo*. Such a teaching could hardly provide the motivation alleged by the Examiner – especially when the person skilled in the art would need to go to the trouble of radioiodinating the inhibitors of Lee on the expectation that they could have only "limited" application in defined circumstances *in vivo*. The alleged motivation therefore does not, in reality exist. Hence, the rejection based on the combinations [Lee + Colucci], [Lee + Colucci + Flanagan] and [Lee + Colucci + Flanagan + Hunter] should also be withdrawn.

3. CLAIM REJECTIONS: 35 USC §102.

Claims 26 and 28 stand newly rejected as lacking novelty over Lee [J.Biol.Chem., 275(21), 16007-16014 (2000)].

Applicants have amended claim 26 to cognate claim 27. Claim 27 has consequently been cancelled. Since the novelty rejection was not cited versus claim 27, revised claim 26 is believed novel over Lee. Hence, the rejection of claims 26 and 28 should be withdrawn.

CONCLUSION.

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application and claims are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

/Craig Bohlken/
Craig Bohlken
Reg. No. 52,628

GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6530